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(54) **NOVEL 9A-AZALIDES**

NEUE 9A-AZALIDE

NOUVEAUX 9A-AZALIDES

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- **WADDELL, S.T. ET AL.: "Synthesis and antibacterial activity of O-methy derivatives of azalide antibiotics: II 6-OMe derivatives via clarithromycin" BIOORG. MED. CHEM. LETT., vol. 8, 1998, pages 1321-6, XP002100546**

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Description

[0001] The invention relates to novel compounds from the class of macrolide antibiotics. Particularly, the invention relates to novel intermediates from the class of 9a-azalides, to their pharmaceutically acceptable addition salts with inorganic or organic acids, to a process for their preparation and to the use thereof as antibiotics or as intermediates for the synthesis of other macrolide antibiotics.

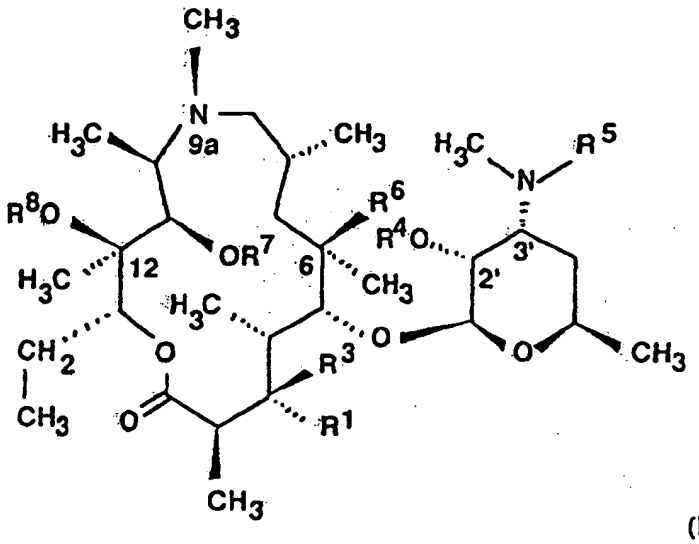
[0002] Macrolide antibiotic erythromycin A has been for more than 40 years considered as a safe and efficient agent for the treatment of respiratory and genital infections caused by Gram-positive and by some Gram-negative bacteria, some species of *Legionella, Mycoplasma, Chlamidia* and *Helicobacter.* Noticed changes in bioavailability after oral administration, gastric intolerance in many patients and loss of activity in an acidic medium whereat the inactive metabolite anhydroerythromycin is formed are basic disadvantages in the clinical use of erythromycin. However, the spirocyclization of the aglycone ring is successfully inhibited by a chemical transformation of C-9 ketone or hydroxyl groups in C-6 and/or C-12 positions. Thus, e.g by oximation of C-9 ketone and subsequent Beckmann rearrangement and reduction, 9-deoxo-9a-aza-9a-homoerythromycin A, the first 15-membered macrolide antibiotic with 9a-amino group incorporated in the aglycone ring, is obtained (Kobrehel G. et al., US 4,328,334; 5/1982). By reductive methylation of 9-amines according to Eschweiler-Clark process, 9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin (AZITHROMYCIN), a prototype of a novel class of macrolide antibiotics, namely azalides, is synthesized (Kobrehel G. et al., BE 892357; 7/1982). In addition to a broad antimicrobial spectrum including also Gram-negative bacteria, azithromycin is also characterized by a long biological half-life, a specific transport mechanism to the place of use and a short therapy period. Azithromycin easily penetrates and it accumulates inside human phagocyte cells resulting in an improved action upon intracellular pathogenic microorganisms from the classes of *Legionella, Chlamidia* and *Helicobacter.*

[0003] Further, it is known that C-6/C-12 spirocyclization of erythromycin A is successfully inhibited by *O*-methylation of C-6 hydroxyl group of the aglycone ring (Watanabe Y. et al., US 4,331,803; 5/1982). By the reaction of erythromycin with benzyloxycarbonyl chloride and subsequent methylation of the obtained 2'-*O*,3'-*N*-bis(benzyloxycarbonyl) derivative, by elimination of the protecting groups and by 3'-*N*-methylation, there are formed, in addition to 6-*O*-methylerythromycin (CLARITHROMYCIN), also significant amounts of 11-*O*-methylerythromycin and of multiple-substituted analogs (Morimoto S., et al., J. Antibiotics, 1984, 37, 187). With respect to erythromycin A, clarithromycin is considerably more stable in an acidic medium and exhibits better *in vitro* action with respect to Gram-positive bacteria strains (Kirst H. A. et al., Antimicrobial Agents and Chemoter., 1989, 1419). In a similar manner also a series of *O*-methyl-derivatives of azithromycin (Kobrehel G. et al., US 5,250,518; 10/1993) was synthesized. Although the main products of *O*-methylation of azithromycin, namely 11-*O*-methyl-azithromycin (Example 8) and 6-*O*-methyl-azithromycin (Example 6) exhibit significant activity against standard bacteria strains and clinical isolates and pharmacokinetic properties similar to those of azithromycin, the obtaining of products in larger quantities represents an additional technical problem due to nonselectivity of *O*-methylation. The determination of the structure of *O*-methyl-derivatives of azithromycin was based on analysis of ^{1}H-^{1}H and ^{1}H-^{13}C 2D NMR spectra (300 MHz). Subsequently, it was additionally determined by long-range NMR spectroscopy that substitution on C-6 hydroxyl group had been erroneously ascribed to azithromycin and that actually 12-*O*-methyl-azithromycin was in question. Further it has been found that the use of suitable protecting groups on hydroxyl groups in 4"- and 11-positions (especially of silyl protecting groups such as tnimethylsilyl groups) results in selective *O*-methylation and makes possible a simple preparation of 12-*O*-methyl-azithromycin (HR 970051 A; 10/97). Later, Waddell S.T. et al., (Biorg. Med. Chem. Letters 8 (1998), 549-555), independently of the latter patent application, established O-methylation of hydroxyl group in C-12 position.

[0004] The subject of the present invention is novel intermediates and process for their preparation for the purpose of an alternative synthesis of O-methyl derivatives of azithromycin.

[0005] Objects of the present invention are also pharmaceutically acceptable addition salts of *O*-methyl derivatives of azithromycin with organic and inorganic acids, methods and intermediates for their preparation, as well as preparation and application methods of pharmaceutical preparations.

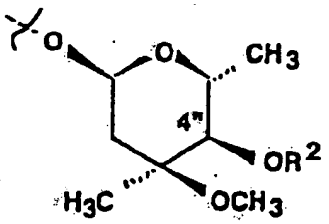
[0006] Novel intermediates from the class of 9a-azalides of the general formula (I)



(I)

characterized in that

R^1 individually stands for L-cladinosyl group of the formula (II)



(II)

wherein

R^2 individually stands for a silyl group,

R^3 individually stands for hydrogen,

R^4 individually stands for hydrogen, or -COO-$(CH_2)_n$-Ar group, wherein n is 1-7 and Ar individually stands for an unsubstituted or substituted aryl group with up to 18 carbon atoms,

R^5 individually stands for hydrogen, methyl group or -COO-$(CH_2)_n$-Ar group, wherein n is 1-7 and Ar individually stands for an unsubstituted or substituted aryl group with up to 18 carbon atoms,

R^6 individually stands for a hydroxyl group,

R^7 individually stands for hydrogen, (C_1-C_{12})alkyl group, silyl group,

R^8 individually stands for hydrogn, (C_1-C_{12})alkyl group,

and their pharmaceutically acceptable addition salts with inorganic or organic acids, are obtained by the following steps.

Step 1:

[0007] Azithromycin of the general formula (I) wherein R^1 stands for L-cladinosyl group of the formula (II), R^2, R^3, R^4, R^7 and R^8 are mutually the same and stand for hydrogen, R^5 is methyl and R^6 is a hydroxyl group, is subjected to a reaction with organic carboxylic acid chlorides of the formula (III)

$ClCOO(CH_2)_n$-Ar (III)

wherein n is 1-7 and Ar individually stands for unsubstituted or substituted aryl groups with up to 18 carbon atoms, preferably with benzyloxycarbonyl chloride, in the presence of bases, preferably sodium hydrogen carbonate, in a reaction-inert solvent, preferably in benzene or toluene, yielding 2'-O,3'-N-bis(bezyloxycarbonyl)-3'-N-demethyl-azithromycin (Kobrehel G. et al., US 5,250,518; 5/1993) of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2, R^3, R^7 and R^8 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group and R^6 is hydroxyl group, which is subsequently subjected to silylation of hydroxyl groups in

A/ 4"- and 11-positions with 2-5 equimolar excess of a silylating agent, in an organic inert solvent, at the temperature of 0-5°C during 5-8 hours, yielding novel 4"- 11-*O*-bis(trimethylsilyl)-2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethylazithromycin of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2 and R^7 are mutually the same and stand for trimethylsilyl group, R^3 and R^8 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group and R^6 is hydroxyl group, or in **B/** 4"-position with 1.1-2 equimolar excess of a silylating agent, in an organic inert solvent, at the temperature of 0-5°C during 1 hour, yielding novel 4"-*O*-trimethyl-silyl-2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethyl-azithromycin of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2 stands for trimethylsilyl group, R^3, R^7 and R^8 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group and R^6 stands for hydroxyl group.

[0008] As silylating agents there are used 1,1, 1,3,3,3-hexamethyldisilazane, trimethylsilyl chloride, bis(trimethylsilyl) acetamide and similar agents for introducing trimethylsilyl group, preferably a mixture of trimethylsilyl chloride and trimethylsilyl imidazole. As a suitable solvent pyridine, ethyl acetate, *N,N*-dimethylformamide, methylene chloride and the like, preferably pyridine are used.

Step 2:

[0009] By a reaction of 4",11-*O*-bis(trimethylsilyl)-2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethyl-azithromycin from the step 1A/ or 4"-*O*-trimethylsilyl-2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethyl-azithromycin from the step 1B/, respectively, with 1.3-10 moles of a corresponding alkylating agent, preferably methylating agent, in the presence of 1.1-8.5 moles of a suitable base, at a temperature from -15°C to room temperature, preferably at 0 - 5°C, in a suitable reaction-inert solvent, there comes to

A/ a selective alkylation, preferably methylation of C-12 hydroxyl group yielding a novel 4"-11-*O*-bis(trimethylsilyl)-2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethyl-12-*O*-methyl-azithromycin of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2 and R^7 are mutually the same and stand for trimethylsilyl group, R^3 stands for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group, R^6 is hydroxyl group and R^8 is methyl, or
B/ an alkylation, preferably methylation of C-1 1 or C-12 hydroxyl group yielding a mixture of novel 4"-*O*-trimethylsilyl-2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethyl-11-*O*-methyl-azithromycin of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2 stands for trimethylsilyl group, R^3 and R^8 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group, R^6 stands for hydroxyl group and R^7 is methyl, or 4"-*O*-trimethylsilyl-2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethyl-12-*O*-methyl-azithromycin of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2 stands for trimethylsilyl group, R^3 and R^7 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group, R^6 stands for hydroxyl group and R^8 is methyl.

[0010] As suitable alkylating agents there are used (C_1-C_{12})alkyl halides, preferably methyl iodide, dimethyl sulfate, methyl methane sulfonate or methyl p-toluene sulfonate, preferably methyl iodide. Suitable bases are alkali metal hydride (lithium hydride, sodium hydride or potassium hydride), alkali metal hydroxide (potassium hydroxide or sodium hydroxide) or alkali metal methyl amide (lithium amide, sodium amide or potassium amide), preferably sodium hydride. Suitable reaction-inert solvents are dimethyl sulfoxide, *N,N* dimethyl formamide, *N,N*-dimethyl acetamide or hexamethyl phosphoric triamide, preferably *N,N* dimethyl formamide, dimethyl sulfoxide or a mixture thereof with tetrahydrofuran.

Step 3:

[0011] 4"-11-*O*-Bis(trimethylsilyl)-2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethyl-12-*O*-methyl-azithromycin from the step 2A/ or the obtained mixture of 4"-*O*-trimethylsilyl-2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethyl-11-*O*-methyl-azithromycin and 4"-*O*-trimethylsilyl-2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethyl-12-*O*-methyl-azithromycin from the step 2B/ is subjected to a hydrogenolysis reaction according to the method by E.H. Flynn et al. (Journal of American Chemical Society, 77, 3104, 1950) in order to deprotect protecting groups on 2'- and 3'-positions and then to desilylation according to the conventional process in lower alcohols, preferably isopropanol in the presence of formic acid in

A/ 4"-and 11-positions in the step 2A/ yielding 3'-*N*-demethyl-12-*O*-methyl-azithromycin of the general formula (1), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2, R^3, R^4, R^5 and R^7 are mutually the same and stand for hydrogen, R^6 is hydroxyl group and R^8 is methyl, or in

B/ 4"-position in the Step 2B/ yielding a mixture of 3'-*N*-demethyl-11-*O*-methyl-azithromycin of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2, R^3, R^4, R^5 and R^8 are mutually the same and stand for hydrogen, R^6 is hydroxyl group and R^7 is methyl, and 3'-*N*-demethyl-12-*O*-methyl-azithromycin of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2, R^3, R^4, R^5 and R^7 are mutually the same and stand for hydrogen, R^6 is hydroxyl group and R^8 is methyl.

[0012] Hydrogenolysis is carried out in a solution of lower alcohols, preferably in ethanol, in the presence of NaOAc/HOAc buffer (pH 5) with a catalyst such as palladium black or palladium on charcoal, at a hydrogen pressure from I to 20 bars, at room temperature.

Step 4:

[0013] 3'-*N*-Demethyl-12-*O*-methyl-azithromycin from the step 3A/ or the obtained mixture of 3'-*N*-demethyl-11-*O*-methyl-azithromycin and 3'-*N*-demethyl-12-*O*-methyl-azithromycin from the Step 3B/ is subjected to a reductive 3'-*N*-methylation with 1-3 equivalents of formaldehide (37%) in the presence of an equal or double quantity of formic acid (98-100%) and hydrogenation catalyst or of some other hydrogen source, in a reaction-inert solvent such as halogenated hydrocarbons, lower alcohols or lower ketones, preferably chloroform, at the reflux temperature of the reaction mixture, yielding - in the case of the compound from the Step 3A/ - -12-*O*-methyl-azithromycin of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2, R^3, R^4 and R^7 are mutually the same and stand for hydrogen, R^5 and R^8 are mutually the same and stand for methyl and R^6 is hydroxyl group, or - in the case of products from the Step 3B/ - a mixture of 11-*O*-methyl-azithromycin of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2, R^3, R^4 and R^8 are mutually the same and stand for hydrogen, R^5 and R^7 are mutually the same and stand for methyl and R^6 is hydroxyl group, and of 12-*O*-methyl-azithromycin of the general formula (I), wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 have the meanings as given in the case of 3'-N-methylation of the compounds from the Step 3A/.

[0014] Pharmaceutically acceptable addition salts, which are another object of the present invention, are obtained by a reaction of the novel compounds of the general formula (I) with an at least equimolar amount of a corresponding inorganic or organic acid such as hydrochloric, hydroiodic, sulfuric, phosphoric, acetic, propionic, trifluoroacetic, maleic, citric, stearic, succinic, ethylsuccinic, methanesulfonic, benzenesulfonic, p-toluenesulfonic, laurylsulfonic and similar acids, in a reaction-inert solvent. The addition salts are isolated by filtration if they are insoluble in the reaction-inert solvent, by precipitation with a nonsolvent or by evaporation of the solvent, most frequently by lyophilization.

[0015] Antibacterial *in vitro* acitivity of the novel compounds of the general formula (I) and their pharmaceutically acceptable addition salts with inorganic or organic acids on a series of standard test-microorganisms was determined in a Mueller-Hinton medium (Difco-Laboratories, Detroit, MI) by a conventional method of double dilution in accordance with recommendations of NCCLS (The National Commitee for Clinical Laboratory Standards). Each test microorganism was inoculated to the final inoculum size of 5×10^5 cfu/ml and the incubation was carried out in an anaerobic manner at 37°C during 18 hours. The MIC in the liquid medium was defined as the lowest concentration of an antibacterial agent inhibiting visible growth in microdilutional containers. Control organisms were obtained from ATCC (The American Type Culture Collection). All standards were identified by a standard procedure and were storaged at -70°C. The results of 12-*O*-methyl-azithromycin on standard test microorganisms and clinical isolates in comparison with azithromycin are shown in Table 1 and Table 2.

[0016] By determining the concentration of 12-*O*-methyl-azithromycin in serum after a single oral dosis of 20 mg/kg on a group of 36 male rats in time intervals from 0.25 to 24 hours it was established that the novel antibiotic was very fast absorbed in the serum. An analysis of the peaks suggested the existence of enterohepatic circulation. During 0.5 and I hours a rapid drop of concentration took place, which was followed by a repeated increase. The maximum sub-

stance concentration was achieved after 2 hours (Cmax 248.8 ng/ml). A secondary maximum was achieved 4 hours after the application. The half-life was 5.2 hours and the total AUC was 1993.4 h ng /ml.

Table 1:

Antibacterial *in vitro* activity of 12-*O*-methyl-azithromycin on standard strains in comparison with azithromycin		
	MIC (mcg/ml)	
Organism	Azithromycin	12-*O*-Methyl-azithromycin
Staphylococcus aureus ATCC 6538 P	1	0.25
S. aureus ATCC 29213	0.25	0.25
S. epidermidis ATCC 12228	0.5	0.03
Micrococcus flavus ATCC 10240	0.5	0.12
M. luteus ATCC 9341	0.06	0.03
Streptococcus faecalis ATCC 8043	0.5	0.25
Bacillus subtilis ATCC 6633	4	1
B. cereus ATCC 11778	1	0.25
Escherichia coli ATCC 10536	1	0.5

Table 2:

Antibacterial *in vitro* activity of 12-*O*-methyl-azithromycin on a series of clinical isolates in comparison with azithromycin				
Organism (No.of strains)	Compound	MIC (µg/ml)		
		Range	50%	90%
Staph. aureus. (77)	Azithromycin	0.25 - 8	1	4
	12-*O*-Methylazithromycin	0.12 - 2	0.25	1
S. epidermidis (20)	Azithromycin	0.25 - 16	0.25	8
	12-*O*-Methylazithromycin	0.12 - 8	0.25	4
Streptococcus pneumoniae (25)	Azithromycin	0.03 - 0.25	0.06	0.12
	12-*O*-Methylazithromycin	0.03 - 0.12	0.03	0.12
Enterococcus sp. (35)	Azithromycin	0.25 - 16	1	16
	12-*O*-Methylazithromycin	0.12 - 8	0.5	8
Haemophilus influenzae (40)	Azithromycin	0.12 - 0.5	0.25	0.5
	12-*O*-Methylazithromycin	0.06 - 0.5	0.12	0.25

[0017] The process for the preparation of novel intermediates from the class of 9a-azalides is illustrated by the following examples, which in no way limit the scope of the invention.

Preparation 1

2'-*O*,3'-*N*-Bis(bezyloxycarbonyl)-3'-*N*-demethyl-azithromycin A

[0018] To a solution of azithromycin (17 g, 0.0227 mole) in toluene (170 ml), $NaHCO_3$ (74.8 g, 0.890 mole) was added and then the reaction mixture was heated under stirring to reflux temperature (80-85°C). To the reaction suspension 102 ml of 50% benzyloxycarbonyl chloride (104.04 g, 0.305 mole) in toluene were added dropwise under stirring during 1 hour. The reaction mixture was stirred at the same temperature for further 2 hours and left standing

over night at room temperature. After filtration the precipitate was rinsed with toluene (85 ml) and the toluene solution was extracted twice with 0.25 *N* HCl (170 ml) and twice with 1.5% aqueous NaCl solution (170 ml). To toluene water was added (340 ml) (pH 3.1), the pH of the reaction mixture was adjusted with 6 N HCl to 2.0, the layers were separated and the organic layer was further extracted three times with water (340 ml) under keeping the pH at 2.0. To combined water extracts CH_2Cl_2 (125 ml) was added, the pH was adjusted with an aqueous NaOH solution (20%) to 10, the layers were separated and the aqueous layer was again extracted with CH_2Cl_2(125 ml). The combined organic extracts were dried over K_2CO_3, filtered and evaporated at a reduced pressure, yielding 16.5 g of a thick oily residue, which was optionally purified with low-pressure chromatography on a silica gel 60 column (230-400 mesh ASTM). For this purpose the crude product was dissolved in CH_2Cl_2 (20 ml) and applied to a silica gel column (50 g) under nitrogen pressure of 0.5 bar. In order to remove the residual benrylchloroformate and its disintegration products, CH_2Cl_2 (150 ml) was led through the column and then by using the solvent system methylene chloride-methanol, 9:1 (200 ml) and evaporating the fractions containing chromatographically homogeneous title product, there were obtained 11.53 g of TLC pure 2'-*O*,3'-*N*-bis-(benzyloxycarbonyl)-*N*-demethyl-azithromycin with physical-chemical constants as described in US patent 5,250,518 of 10/1993.

Example 1

4",11-*O*-Bis(trimethytsilyl)-2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethyl-azithromycin

[0019] To a solution of 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethyl-azithromycin (5.0 g, 0,005 mole) in pyridine (50 ml), cooled to 0-5°C, trimethylsilylimidazole (3.3 ml, 0.0226 mole) and trimethylsilylchloride (3.0 ml, 0.0179 mole) were added under nitrogen stream. The reaction mixture was stirred at the same temperature for 6 hours, n-hexane (60 ml) and water (100 ml) were added, the layers were separated and the organic layer was rinsed with a saturated $NaHCO_3$ solution (60 ml) and water (60 ml). After drying over $MgSO_4$, filtration and evaporation of the solvent at a reduced pressure, 5.48 g of a white amorphous precipitate were obtained, which were optionally purified by low-pressure chromatography on a silica gel column using the system CH_2Cl_2-CH_3OH, 9:1. The combining and evaporation of chromatographically homogeneous fractions gave the title product with the following physical-chemical constants:

TLC,	Methylene chloride-methanol, 90:1	Rf 0.875
	Ethyl acetate-N-hexane-diethyl amine, 100:100:20	Rf 0.942

(IR (KBr) cm^{-1}: 3524, 2969, 2692, 1754, 1732, 1708, 1498, 1456, 1382, 1335, 1252, 1168, 1116, 1060, 1005, 895, 841, 754, 696.

^1H NMR (300 MHz, $CDCl_3$) δ: 7.32-7.23 (Ph), 5.12, 4.98 (CH_2-Ph), 4.85 (H-1"), 4.70 (H-1'), 4.65 (H-2'), 4.46 (H-3'), 4.26 (H-5"), 4.42 (H-3), 3.72 (H-5'), 3.66 (H-11), 3.49, 3.47 (H-5), 3.20 (H-4"), 3.32, 3.18 (3"-OCH_3), 2.83, 2.79 (3'-NCH_3), 2.78 (H-2), 2.64 (H-10), 2.35 (H-9a), 2.33 (H-2"a), 2.11 (9a-NCH_3), 1.94 (H-9b), 1.91 (H-8), 1.64 (H-14a), 1.94 (H-4), 1.50 (H-2"b), 1.50 (H-14b), 1.27, 1.25 (6-CH_3), 1.24 (5"-CH_3), 1.19 (5'-CH_3), 1.12 (3"-CH_3), 1.16 (12-CH_3), 1.26 (2-CH_3), 0.89 (10-CH_3), 0.95 (8-CH_3), 0.85 (14-CH_3), 1.02 (4-CH_3), 1.02 (4-CH_3), 0.16 (11-$OSi(CH_3)_3$, and 0.13 /4"-$OSi(CH_3)_3$/.

^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.2 (C-1), 156.2, 156.4 (*OCO*), 154.5, 154.4 (*NCO*), 136.7-127.5 (Ph), 100.2 (C-1'), 97.3 (C-1"), 83.9 (C-5), 80.7 (C-4"), 75.0 (C-3), 75.0 (C-2'), 75.3 (C-6), 73.2 (C-3"), 69.4, 69.2, 67.1, 66.8 (*CH_2*-Ph), 64.8 (C-5"), 62.3 (C-10), 54.8 (C-3'), 49.4, 49.2 (3"-OCH_3), 46.2 (C-2), 38.5 (C-7), 39.4 (C-4), 34.2 (9a-NCH_3), 35.9, 35.6 (C-2"), 36.2, 36.1 (C-4'), 29.0 (3'-NCH_3), 25.6 (C-8), 27.8 (6-CH_3), 21.9 (3"-CH_3), 21.5 (8-CH_3), 20.7 (5'-CH_3), 23.4 (C-14), 18.4 (5"-CH_3), 16.0 (2-CH_3), 11.6 (14-CH_3), 9.6, 9.5 (4-CH_3), 8.3 (10-CH_3), 1.2 /11-$OSi(CH_3)/_3$ and 0.67 /4"-$OSi(CH_3)_3$/.

ES-MS 1147

Example 2

3'-*N*-Demethyl-12-*O*-methyl-azithromycin

[0020] To a solution of the product from Example 1 (1.0 g, 0.0009 mole) in *N*,*N*-dimethyl-formamide (20 ml) methyl iodide (0.43 ml, 0.0069 mole) and 60% sodium hydride (0.23 g, 0.0058 mole) were gradually added during 3 hours at room temperature. The reaction mixture was stirred for further 30 minutes at the same temperature, the reaction was stopped by the addition of triethyl amine (2 ml), it was transferred into a mixture of 10% aqueous $NaHCO_3$ solution (50 ml) and water (50 ml) and extracted with ethyl acetate. The combined organic extracts were rinsed with a saturated NaCl solution and water, dried over $MgSO_4$, filtered and evaporated at a reduced pressure, yielding 0.93 g of a yellow

precipitate [Rf 0.832, methylene chloride-methanol, 90:1; IR (KBr) cm^{-1}: 3516, 1752, 1732, 1705, 1456, 1382, 1336, 1253, 1169, 1116, 1062, 1004, 896, 840, 754, 696]. The product was dissolved in ethanol (20 ml), NaOAc/HOAc buffer with pH 5 (0.17 ml acetic acid, 0.263 g sodium acetate, 0.22 ml ethanol and 1 ml water) and Pd/C 10% (0.6 g) were added, and the reaction mixture was hydrogenated under stirring for 5 hours in an autoclave at a hydrogen pressure of 5 bars. The catalyst was filtered off, the filtrate was evaporated to a thick syrup, CH_2Cl_2 (10 ml) and water (15 ml) were added, the pH of the mixture was adjusted with 2 *N* HCl to 4, the layers were separated and the aqueous layer was, upon adjustment to pH 9.5 with 20% NaOH, extracted with CH_2Cl_2 (3x10 ml). The combined organic extracts were dried over K_2CO_3, filtered and evaporated. The precipitate was dissolved in isopropanol (10 ml), water (10 ml) and some drops of formic acid were added and it was stirred for 30 minutes at room temperature, extracted with isopropyl acetate at pH 9.5, which upon evaporation at a reduced pressure yielded 0.43 g of the title product with the following physical-chemical constants:
IR (KBr) cm^{-1}: 3672, 3496, 2962, 1727, 1458, 1375, 1343, 1280, 1263, 1118, 1085, 1048, 1005, 998.
^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.4 (C-1), 102.7 (C-1'), 95.5 (C-1"), 83.4 (C-5), 79.7 (C-12), 78.0 (C-3), 76.6 (C-11), 74.0 (C-13), 73.9 (C-6), 74.3 (C-2'), 73.0 (C-3"), 68.8 (C-9), 65.7 (C-5"), 60.1 (C-3'), 61.2 (C-10), 52.8 (12-OCH_3), 49.8 (3"-OCH_3), 45.5 (C-2), 41.5 (C-4), 33.1, 3'-NCH_3, 36.8 (9a-NCH_3), 35.1 (C-2"), 28.8 (C-4'), 27.0 (C-8).
EI-MS m/z 748.

Example 3

12-*O*-Methyl-azithromycin

[0021] To a solution of 3'-*N*-demethyl-12-*O*-methyl-azithromycin from Example 2 (0.43 g, 0.0006 mole) in $CHCl_3$ (20 ml), formaldehyde (37%) (0.047 ml, 0.0006 mole) and formic acid (98-100%) (0.042 ml, 0.0011 mole) were added. The reaction mixture was stirred for 3 hours under reflux, cooled to room temperature, poured onto water (20 ml) and upon adjustment of pH to 4.0, the layers were separated and the aqueous layer was extracted two more times with $CHCl_3$. To the aqueous layer $CHCl_3$ was added, the pH was adjusted to 9.5 (2*N* NaOH), the layers were separated and the aqueous one was extracted two more times with $CHCl_3$. The combined organic extracts at pH 9.5 were dried (K_2CO_3) and evaporated, yielding 0.38 g of the title product, which was, if necessary, purified by a chromatography on a silica gel column using the system CH_2Cl_2-CH_3OH-conc.NH_4OH, 90:9:1.

TLC,	Methylene chloride-methanol-conc. ammonia,	90:9:0.5	Rf 0.363
	Ethyl acetate-N-hexane-diethyl amine,	100:100:20	Rf 0.745

IR (KBr) cm^{-1}: 3499, 2972, 2940, 1736, 1633, 1460, 1381, 1259, 1168, 1110, 1059, 1082,1054,1013,999.
^1H NMR (300 MHz, $CDCl_3$) δ: 5.39 (H-13), 5.00 (H-1"), 4.43 (H-1'), 4.32 (H-3), 4.06 (H-5"), 3.68 (H-11), 3.65 (H-5), 3.51 (H-5'), 3.38 (12-OCH_3), 3.32 (3"-OCH_3), 3.24 (H-2'), 3.02 (H-4"), 2.73 (H-2), 2.69 (H-10), 2.49 (H-3'), 2.34 (H-2"a), 2.31 (H-9a), 2.29 /3'N(CH_3)$_2$/, 2.30 (9a-NCH_3), 2.12 (H-9b), 2.04 (H-4), 2.01 (H-8), 1.73 (H-14a), 1,68 (H-4'a), 1.66 (H-7a), 1.56 (H-2"b), 1.52 (H-14b), 1.36 (H-7b), 1.29 (6-CH_3), 1.21 (2-CH_3), 1.30 (5"-CH_3), 1.24 (H-4'b), 1.23 (3"-CH_3), 1.22 (5'-CH_3), 1.09 (12-CH_3), 1.29 (4-CH_3), 1.09 (10-CH_3), 0.92 (8-CH_3), 0.93 (14-CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5 (C-1), 103.1 (C-1'), 95.2 (C-1"), 83.6 (C-5), 79.2 (C-12), 78.1 (C-3), 76.6 (C-11), 74.7 (C-13), 73.8 (C-6), 70.9 (C-2'), 68.8 (C-9), 65.6 (C-5"), 65.7 (C-3'), 61.6 (C-10), 52.8 (12-OCH_3), 49.4 (3"-OCH_3), 45.1 (C-2), 43.0 (C-7), 41.8 (C-4), 40.4 /3'N(CH_3)$_2$/, 36.8 (9a-NCH_3), 35.0 (C-2"), 29.0 (C-4'), 26.9 (C-8), 26.9 (6-CH_3), 22.0 (8-CH_3), 22.0 (C-14), 21.6 (3"-CH_3), 21.3 (5'-CH_3), 18.1 (5"-CH_3), 16.9 (12-CH_3), 14.6 (2-CH_3), 11.0 (14-CH_3), 9.6 (4-CH_3), 9.4 (10-CH_3).

Example 4

4"-*O*-Trimethylsilyl-2'-*O*-3'-*N*-bis(benzyloxycarbonyl)-3'-*N* demethyl-azithromycin

[0022] To a solution of 2'-*O*,3'-*N*-bis(benzyloxycarbonyl)-3'-*N*-demethyl-azithromycin (5 g, 0.005 mole) in pyridine (30 ml) cooled to 0-5°C, trimethylsilyl imidazole (1.46 ml, 0.01 mole) and trimethylsilyl chloride (1.64 ml, 0.01 mole) were added under a nitrogen stream. The reaction mixture was stirred for 1 hour at the same temperature, n-hexane (50 ml) and water (25 ml) were added, the layers were separated and the organic one was rinsed with a saturated $NaHCO_3$ solution (25 ml) and water (25 ml). After drying over $MgSO_4$, filtration and evaporation of the solvent at a reduced pressure there was obtained an amorphous precipitate (3.65 g), which was optionally purified by low-pressure chromatography on a silica gel column using the system methylene chloride-methanol-conc. ammonia, 90:9:0.5. By combining and evaporating the chromatographically homogeneous fractions with Rf 0.670 there was obtained the title

product with the following physical-chemical constants:

TLC,	Methylene chloride-methanol,	90:1	Rf 0.525
	Ethyl acetate-N-hexane-diethyl amine,	100:100:20	Rf 0.862

IR (KBr) cm^{-1}: 3502, 2969, 2938, 1753, 1732, 1708, 1454, 1383, 1365, 1254, 1169, 1118, 1063, 1001, 897, 839, 754, 696.

^1H NMR (300 MHz, $CDCl_3$) δ: 7.34-7.26 (Ph), 5.13, 5.09, (CH_2-Ph), 5.07 (H-1"), 4.78 (H-1'), 4.68 (H-13), 4.66 (H-2'), 4.55 (H-3'), 4.22 (H-5"), 4.13 (H-3), 3.96 (H-5'), 3.65 (H-11), 3.58, 3.54 (H-5), 3.15 (H-4"), 3.37, 2.99 (3"-OCH_3), 2.85, 2.81 (3'-NCH_3), 2.70 (H-2), 2.68 (H-10), 2.54 (H-9a), 2.35 (H-2"a), 2.31 (9a-NCH_3), 2.04 (H-9b), 1.97 (H-8), 1.90 (H-14a), 1.85 (H-4), 1.62 (H-7a), 1.50 (H-2"b), 1.44 (H-14b), 1.28, 1.27 (6-CH_3), 1.23 (5"-CH_3), 1.16 (5'-CH_3), 1.15 (H-7b), 1.04 (3"-CH_3), 1.15 (12-CH_3), 1.10 (2-CH_3), 1.10 (10-CH_3), 0.92 (8-CH_3), 0.89 (14-CH_3), 1.10 (4-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.8 (C-1), 156.6, 156,3 (*OCO*), 154.7, 154.6 (*NCO*), 136.8-127-5 (Ph), 99.2 (C-1'), 94.8 (C-1'"), 83.2, 83.1 (C-5), 80.5, 80.4 (C-4"), 77.3 (C-3), 75.1, 75.0 (C-2'), 74.1 (C-12), 73.8 (C-11), 73.2 (C-6), 73.2 (C-3"), 69.2, 69.0, 67.2, 66.8 (*CH_2*-Ph), 64.8 (C-5"), 62.2 (C-10), 54.6 (C-3'), 49.3, 48.8 (3"-OCH_3), 44.7 (C-2), 41.5 (C-7), 41.1 (C-4), 36.1 (9a-NCH_3), 35.1, 35.0 (C-2"), 36.3, 35.7 (C-4'), 28.4 (3'-NCH_3), 26.3 (C-8), 26.8 (6-CH_3), 22.1 (3"-CH_3), 21.6 (8-CH_3), 21.4 (5'-CH_3), 21.0 (C-14), 18.7 (5"-CH_3), 15.9 (2-CH_3), 14.5 (12-CH_3), 11.0 (14-CH_3), 8.5 (4-CH_3), 7.1 (10-CH_3), 0.63/4"-$OSi(CH_3)_3$/.

ES-MS 1075.

Example 5

11-*O*-methyl-azithromycin and 12-*O*-methyl azithromycin

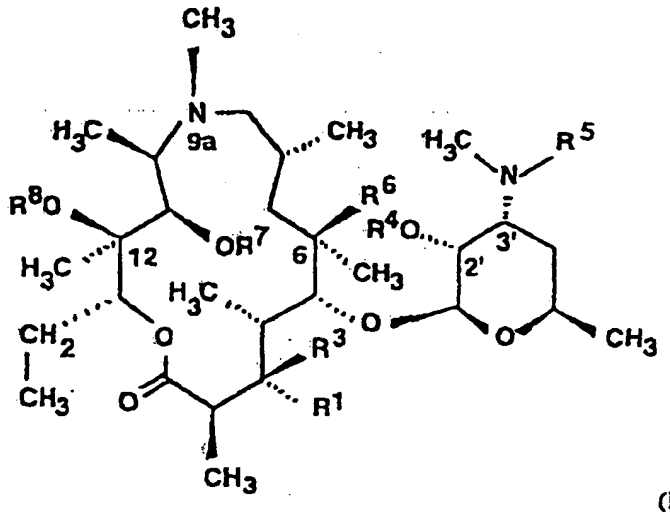
[0023] To a solution of the product from Example 4 (3.0 g, 0.0028 mole) in *N,N*-dimethylformamide (50 ml), methyl iodide (1.29 ml, 0.0207 mole) and 60% sodium hydride (0.69 g, 0.0174 mole) were gradually added over 3 hours at room temperature.

[0024] The reaction mixture was stirred for 1 hour at the same temperature, the reaction was stopped by addition of triethylamine (5 ml), it was transferred into a mixture of 10% aqueous $NaHCO_3$ solution (100 ml) and water (100 ml) and extracted with ethyl acetate. The combined organic extracts were rinsed with a saturated NaCl solution and water and dried over $MgSO_4$, filtered and evaporated at a reduced pressure yielding 2.9 g of a mixture of products, which was optionally purified by low-pressure chromatography on a silica gel column using the system methylene chloride-methanol, 90:1, yielding a chromatographically homogeneous 4"-O-trirnethylsilyl-2'-O-3'-*N*-bis(benzyloxy-carbonyl)-3'-*N*-demethyl-11-O-methyl-azithromycin with Rf 0.745 [IR (KBr): 3452, 2969, 1752, 1736, 1706, 1455, 1382, 1332, 1254, 1169, 1117, 1063. 1002, 914, 897, 840, 754, 697] and 4"-O-trimethylsilyl-2'-O-3')-*N*-bis(benzyloxy-carbonyl)-3'-*N* demethyl-12-O-methyl-azithromycin with Rf 0.485 [IR (KBr): 3450, 2958, 1754, 1718, 1708, 1458, 1383, 1252, 1168, 1068, 1010, 896, 842, 753, 695].

[0025] The obtained mixture was dissolved in ethanol (50 ml), NaOAc/HOAc buffer with pH 5 (0.51 ml HOAc, 0.789 g NaOAc, 0.66 ml ethanol and 3 ml water) and 10% Pd/C (1.5 g) were added and the mixture was hydrogenated under stirring for 8 hours in an autoclave at a hydrogen pressure of 5 bars. The catalyst was filtered off, the filtrate was evaporated to a thick syrup, water (50 ml) and $CHCl_3$ (50 ml) were added and the product was isolated by a pH gradient extraction at pH 4.0 and 9.5. The combined organic extracts at pH 9.5 were dried over K_2CO_3 and evaporated to an amorphous precipitate. The precipitate was dissolved in isopropanol (20 ml), water (20 ml) and some drops of formic acid were added and it was stirred for 30 minutes at room temperature, extracted with isopropyl acetate at pH 9.5, dried over sodium sulfate and evaporated at a reduced pressure. The obtained product was dissolved in $CHCl_3$ (50 ml), formaldehyde (37%) (0.24 ml) and formic acid (98-100%) (0.22 ml) were added. The reaction mixture was stirred for 3 hours under reflux, cooled to room temperature, poured onto water (20 ml) and after adjusting the pH to 4.0 the layers were separated and the aqueous one was extracted two more times with $CHCl_3$. To the water layer $CHCl_3$ was added, pH was adjusted to 9.5 (2 *N* NaOH), the layers were separated and the aqueous one was extracted two more times with $CHCl_3$. The combined organic extracts at pH 9.5 were dried (K_2CO_3) and evaporated, yielding 1.25 g of a precipitate, which was chromatographed on a silica gel column using the system methylene chloride-methanol-conc. ammonia, 90:9:1, yielding 0.40 g of chromatographically homogeneous 11-O-methyl-azithromycin with physical-chemical constants as given in US patent 5,250,518 of 10/1993 and 0.52 g of 12-O-methyl-azithromycin with physical-chemical constants as given in Example 3.

Claims

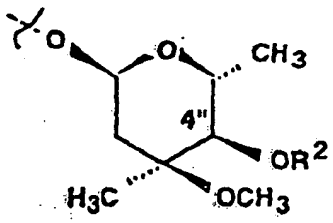
1. Compound of the general formula (I)



(I)

characterized in that

R^1 individually stands for L-cladinosyl group of the formula (II)



(II)

wherein

R^2 individually stands for a silyl group,
R^3 individually stands for hydrogen,

R^4 individually stands for hydrogen, -COO-$(CH_2)_n$-Ar group, wherein n is 1-7 and Ar individually stands for an unsubstituted or substituted aryl group with up to 18 carbon atoms,
R^5 individually stands for hydrogen, methyl group or -COO-$(CH_2)_n$-Ar group, wherein n is 1-7 and Ar individually stands for an unsubstituted or substituted aryl group with up to 18 carbon atoms,
R^6 individually stands for hydroxyl group,
R^7 individually stands for hydrogen, $(C_1\text{-}C_{12})$alkyl group, silyl group,
R^8 individually stands for hydrogen, $(C_1\text{-}C_{12})$alkyl group,

and its phamaceutically acceptable addition salts with inorganic or organic acids.

2. Compound according to claim 1, **characterized in that** R^1 stands for L-cladinosyl group, R^2 and R^7 are mutually

the same and stand for trimethylsilyl group, R^3 and R^8 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group and R^6 is hydroxyl group.

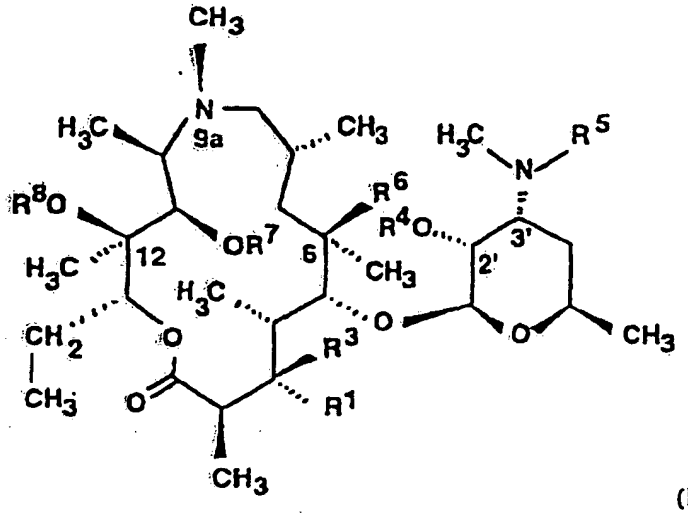
3. Compound according to claim 1, **characterized in that** R^1 stands for L-cladinosyl group, R^2 stands for trimethylsilyl group, R^3, R^7 and R^8 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group and R^6 is hydroxyl group.

4. Compound according to claim 1, **characterized in that** R^1 stands for L-cladinosyl group, R^2 and R^7 are mutually the same and stand for trimethylsilyl group, R^3 stands for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group, R^6 is hydroxyl group and R^8 is methyl.

5. Compound according to claim 1, **characterized in that** R^1 stands for L-cladinosyl group, R^2 stands for trimethylsilyl group, R^3 and R^6 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group, R^6 stands for hydroxyl group and R^7 is methyl.

6. Compound according to claim 1, **characterized in that** R^3 stands for L-cladinosyl group, R^2 stands for trimethylsilyl group, R^3 and R^7 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group, R^6 is hydroxyl group and R^8 is methyl.

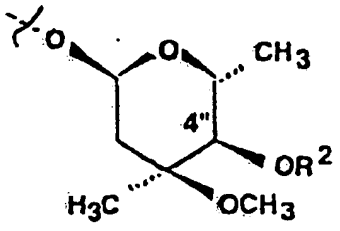
7. Process for the preparation of 12-O-methylazithromycin and/or 11-O-methylazithromycin and their pharmaceutically acceptable addition salts with inorganic or organic acids, **characterized in that** azithromycin of the formula (I)



(I)

wherein

R^1 individually stands for L-cladinosyl group of the formula (II)



(II)

and R^2, R^3, R^4, R^7 and R^8 are mutually the same and stand for hydrogen, R^5 is methyl and R^6 is hydroxyl group, is subjected to a reaction with organic carboxylic acid chlorides of the formula (III)

$$ClCOO(CH_2)_n\text{-}Ar \qquad (III)$$

wherein n is 1-7 and Ar individually stands for unsubstituted or substituted aryl group with up to 18 carbon atoms, preferably with benzyloxycarbonyl chloride, in the presence of bases, preferably sodium hydrogen carbonate, in a reaction-inert solvent, preferably in benzene or toluene, yielding a compound of the general formula (I), wherein R^1 stands for L-cladinosyl group of formula (II), R^2, R^3, R^7 and R^8 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group and R^6 is hydroxyl group,
which is subsequently subjected to a selective silylation of hydroxyl groups in

A/ 4"- and 11-positions with 2-5 equimolar excess of a silylating agent, preferably with a mixture of trimethylsilyl chloride and trimethylsilyl imidazole, in an organic inert solvent such as pyridine, ethyl acetate, *N,N* dimethyl formamide or methylene chloride, preferably in pyridine, at a temperature 0-5°C during 5-8 hours, yielding a compound of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2 and R^7 are mutually the same and stand for trimethylsilyl group, R^3 and R^8 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group and R^6 is hydroxyl group, or in

B/ 4"-position with 1.1-2 equimolar excess of a silylating agent, in an organic inert solvent, preferably in pyridine, at a temperature 0-5°C, during 1 hour, yielding a compound of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2 stands for trimethylsilyl group, R^3, R^7 and R^8 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group and R^6 stands for hydroxyl group,

which are then subjected to *O*-alkylation with 1.3 to 10 molar excess of corresponding alkylating agent, preferably methylating agent, preferably methyl iodide in the presence of 1.1-8.5 moles of a suitable base such as alkali metal hydrides, preferably sodium hydride, in a reaction-inert solvent such as dimethyl sulfoxide, tetrahydrofuran, N,N-dimethyl formamide or a mixture thereof, at a temperature from -15°C to room temperature, preferably at 0-5°C, yielding in the case of

A/ a compound of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2 and R^7 are mutually the same and stand for trimethylsilyl group, R^3 stands for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group, R^6 is hydroxyl group and R^8 is methyl, or in the case of

B/ a mixture of a compound of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2 stands for trimethylsilyl group, R^3 and R^8 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group, R^6 stands for hydroxyl group and R^7 is methyl, and of a compound of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2 stands for trimethylsilyl group, R^3 and R^7 are mutually the same and stand for hydrogen, R^4 and R^5 are mutually the same and stand for benzyloxycarbonyl group, R^6 is hydroxyl group and R^8 is methyl,

which are then subjected to deprotection of the protecting groups in 2'- and 3'-positions in a solution of lower alcohols, preferably ethanol, in the presence of NaOAc/HOAc buffer (pH 5) and of a catalyst in hydrogen atmosphere at a pressure of 1-20 bars and then after isolation, to desilylation in 4"- and 11-positions in lower alcohols, preferably isopropanol, in the presence of formic acid, yielding in the case of

A/ a compound of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2, R^3, R^4, R^5 and R^7 are mutually the same and stand for hydrogen, R^6 is hydroxyl group and R^8 is methyl, or in the case of

B/ a mixture of a compound of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2, R^3, R^4, R^5 and R^8 are mutually the same and stand for hydrogen, R^6 is hydroxyl group and R^7 is methyl, and of a compound of the general formula (I), wherein R^1, R^2, R^3, R^4, R^5, R^7 and R^8 have the meanings as given for deprotection in the case of **A/**,

which are then subjected to reductive 3'-*N*-methylation with 1-3 equivalents of formaldehyde (37%) in the presence of an equal or double quantity of formic acid (98-100%) and hydrogenation catalyst or of some other hydrogen

source, in a reaction-inert solvent, preferably chlorofom, at an elevated temperature, preferably at reflux temperature, yielding in the case of

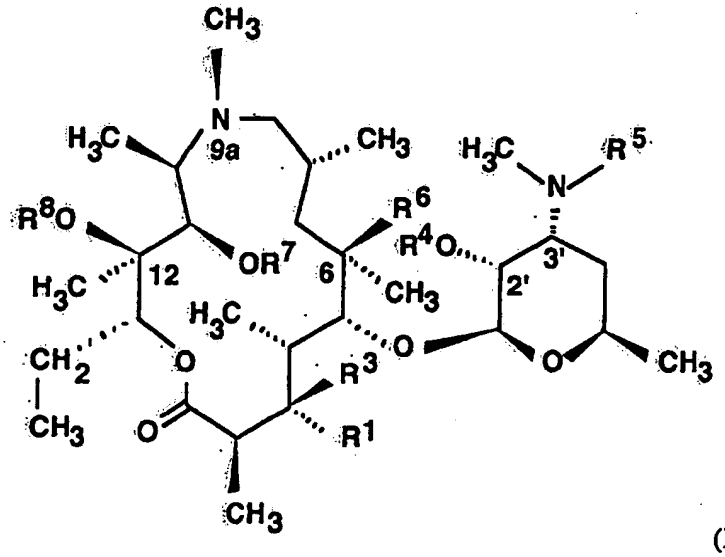
A/ a compound of the general formula (I), wherein R^1 stands for L-cladinosyl group of the formula (II), R^2, R^3, R^4 and R^7 are mutually the same and stand for hydrogen, R^5 and R^8 are mutually the same and stand for methyl and R^6 is hydroxyl group, or in the case of

B/ a mixture of a compound of the general formula (I), wherein R' stands for L-cladinosyl group of the formula (II), R^2, R^3, R^4 and R^8 are mutually the same and stand for hydrogen, R^5 and R^7 are mutually the same and stand for methyl and R^6 is hydroxyl group, and of a compound of the general formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^7 and R^8 have the meanings as given for 3'-N-methylation in the case of **A/**, which is then optionally subjected to separation on a silica gel column, yielding a chromatographically homogeneous compound of the general formula (I), wherein R^1 stands for L-cladinosyl group, R^2, R^3, R^4 and R^8 are mutually the same and stand for hydrogen, R^5 and R^7 are mutually the same and stand for methyl and R^6 stands for hydroxyl group (11-*O*-methyl-azithromycin) and a compound of the general formula (I), wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 have the meanings as given for 3'-N-methylation in the case of **A/** (12-*O*-methyl azithromycin),

8. Pharmaceutical composition useful in the treatment of bacterial infections in humans and animals comprising antibacterially effective amounts of the compound of the general formula (I) or its pharmaceutically acceptable addition salts according to claim 1 in a combination with pharmaceutically acceptable carrier.

Patentansprüche

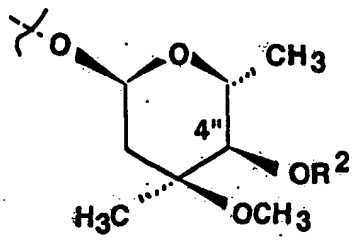
1. Verbindung der allgemeinen Formel (I)



(I)

dadurch gekennzeichnet, dass

R^1 jeweils für L-Cladinosylgruppe der Formel (II)



(II)

steht, worin

- R^2 jeweils für Silylgruppe steht,
- R^3 jeweils für Wasserstoff steht,
- R^4 jeweils für Wasserstoff oder -COO-$(CH_2)_n$-Ar-Gruppe steht, worin n 1-7 ist und Ar jeweils für nichtsubstituierte oder substituierte Arylgruppe mit bis zu 18 Kohlenstoffatomen steht,
- R^5 jeweils für Wasserstoff, Methylgruppe oder -COO-$(CH_2)_n$-Ar-Gruppe steht, worin n 1-7 ist und Ar jeweils für nichtsubstituierte oder substituierte Arylgruppe mit bis zu 18 Kohlenstoffatomen steht,
- R^6 jeweils für Hydroxylgruppe steht,
- R^7 jeweils für Wasserstoff, (C_1-C_{12})Alkylgruppe, Silylgruppe steht,
- R^8 jeweils für Wasserstoff, (C_1-C_{12})Alkylgruppe steht,

und ihre pharmazeutisch annehmbaren Additionssalze mit anorganischen oder organischen Säuren.

2. Verbindung gemäß Anspruch 1, **dadurch gekennzeichnet, dass** R^1 für L-Cladinosylgruppe steht und R^2 und R^7 einander gleich sind und für Trimethylsilylgruppe stehen, R^3 und R^8 einander gleich sind und für Wasserstoff stehen, R^4 und R^5 einander gleich sind und für Benzyloxycarbonylgruppe stehen und R^6 Hydroxylgruppe ist.

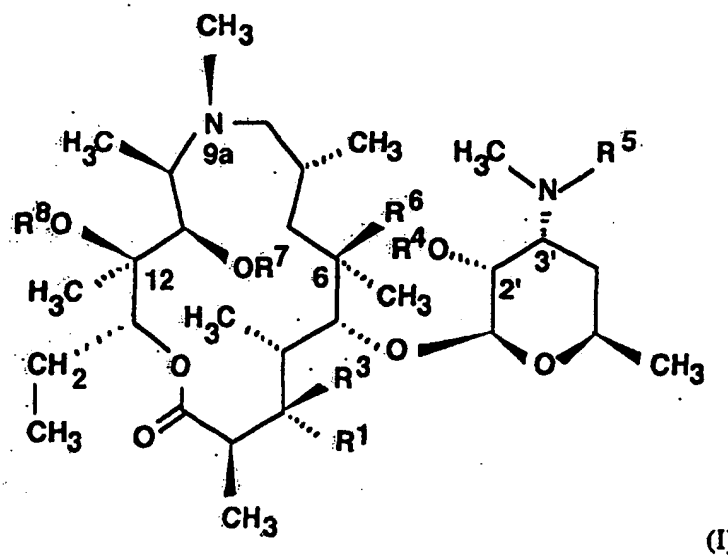
3. Verbindung gemäß Anspruch 1, **dadurch gekennzeichnet, dass** R^1 für L-Cladinosylgruppe steht, R^2 für Trimethylsilylgruppe steht, R^3, R^7 und R^8 einander gleich sind und für Wasserstoff stehen, R^4 und R^5 einander gleich sind und für Benzyloxycarbonylgruppe stehen und R^6 Hydroxylgruppe ist.

4. Verbindung gemäß Anspruch 1, **dadurch gekennzeichnet, dass** R^1 für L-Cladinosylgruppe steht, R^2 und R^7 einander gleich sind und für Trimethylsilylgruppe stehen, R^3 für Wasserstoff steht, R^4 und R^5 einander gleich sind und für Benzyloxycarbonylgruppe stehen, R^6 Hydroxylgruppe ist und R^8 Methyl ist.

5. Verbindung gemäß Anspruch 1, **dadurch gekennzeichnet, dass** R^1 für L-Cladinosylgruppe steht, R^2 für Trimethylsilylgruppe steht, R^3 und R^8 einander gleich sind und für Wasserstoff stehen, R^4 und R^5 einander gleich sind und für Benzyloxycarbonylgruppe stehen, R^6 für Hydroxylgruppe steht und R^7 Methyl ist.

6. Verbindung gemäß Anspruch 1, **dadurch gekennzeichnet, dass** R^1 für L-Cladinosylgruppe steht, R^2 für Trimethylsilylgruppe steht, R^3 und R^7 einander gleich sind und für Wasserstoff stehen, R^4 und R^5 einander gleich sind und für Benzyloxycarbonylgruppe stehen, R^6 Hydroxylgruppe ist und R^8 Methyl ist.

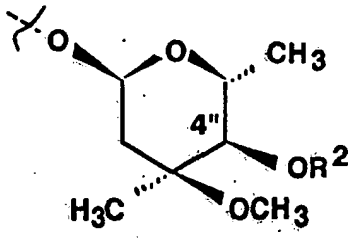
7. Verfahren zur Herstellung von 12-O-Methylazithromycin und/oder 11-O-Methylazithromycin und ihren pharmazeutisch annehmbaren Additionssalzen mit anorganischen oder organischen Säuren, **dadurch gekennzeichnet, dass** Azithromycin der Formel (I)



(I)

worin

R^1 jeweils für L-Cladinosylgruppe der Formel (II)



(II)

steht,
und R^2, R^3, R^4, R^7und R^8 einander gleich sind und für Wasserstoff stehen, R^5 Methyl ist und R^6 Hydroxylgruppe ist,

einer Umsetzung mit organischen Carbonsäurechloriden der Formel (III)

$$ClCOO(CH_2)_n\text{-}Ar \qquad (III)$$

worin n 1-7 ist und Ar jeweils für nichtsubstituierte oder substituierte Arylgruppe mit bis zu 18 Kohlenstoffatomen steht, vorzugsweise mit Benzyloxycarbonylchlorid, in Anwesenheit von Basen, vorzugsweise von Natriumhydrogencarbonat, in einem reaktionsinerten Lösungsmittel, vorzugsweise in Benzol oder Toluol, unterworfen wird, wobei eine Verbindung der allgemeinen Formel (I), worin R^1 für L-Cladinosylgruppe der Formel (II) steht, R^2, R^3, R^7 und R^8 einander gleich sind und für Wasserstoff stehen, R^4 und R^5 einander gleich sind und für Benzyloxycarbonylgruppe stehen und R^6 Hydroxylgruppe ist, erhalten wird,
welche Verbindung anschließend einer selektiven Silylierung der Hydroxylgruppen in

A/ 4"- und 11-Stellungen mit einem 2-5-äquimolaren Überschuß des Silylierungsmittels, vorzugsweise mit

einem Gemisch von Trimethylsilylchlorid und Trimethylsilylimidazol, in einem organischen inerten Lösungsmittel wie Pyridin, Ethylacetat, *N,N*-Dimethylformamid oder Methylenchlorid, vorzugsweise in Pyridin, bei einer Temperatur von 0-5°C während 5-8 Stunden unterworfen wird, wobei eine Verbindung der allgemeinen Formel (I), worin R^1 für L-Cladinosylgruppe der Formel (II) steht, R^2 und R^7 einander gleich sind und für Trimethylsilylgruppe stehen, R^3 und R^8 einander gleich sind und für Wasserstoff stehen, R^4 und R^5 einander gleich sind und für Benzyloxycarbonylgruppe stehen und R^6 Hydroxylgruppe ist, erhalten wird, oder in

B/ 4"-Stellung mit einem 1,1 - 2-äquimolaren Überschuß des Silylierungsmittels in einem organischen inerten Lösungsmittel, vorzugsweise in Pyridin, bei einer Temperatur von 0-5°C während 1 Stunde unterworfen wird, wobei eine Verbindung der allgemeinen Formel (I), worin R^1 für L-Cladinosylgruppe der Formel (II) steht, R^2 für Trimethylsilylgruppe steht, R^3, R^7 und R^8 einander gleich sind und für Wasserstoff stehen, R^4 und R^5 einander gleich sind und für Benzyloxycarbonylgruppe stehen und R^6 für Hydroxylgruppe steht, erhalten wird,

welche Verbindungen anschließend einer O-Alkylierung mit einem 1,3 bis 10-molaren Überschuß eines entsprechenden Alkylierungsmittels, vorzugsweise eines Methylierungsmittels, vorzugsweise Methyliodid, in Anwesenheit von 1,1 - 8,5 Mol einer geeigneter Base wie Alkalimetallhydriden, vorzugsweise Natriumhydrid, in einem reaktionsinerten Lösungsmittel wie Dimethylsulfoxid, Tetrahydrofuran, *N,N*-Dimethylformamid oder einem Gemisch davon, bei einer Temperatur von -15°C bis Raumtemperatur, vorzugsweise bei 0-5°C, unterworfen werden, wobei im Fall von

A/ eine Verbindung der allgemeinen Formel (I), worin R^1 für L-Cladinosylgruppe der Formel (II) steht, R^2 und R^7 einander gleich sind und für Trimethylsilylgruppe stehen, R^3 für Wasserstoff steht, R^4 und R^5 einander gleich sind und für Benzyloxycarbonylgruppe stehen, R^6 Hydroxylgruppe ist und R^8 Methyl ist, erhalten wird, oder im Fall von

B/ ein Gemisch einer Verbindung der allgemeinen Formel (I), worin R^1 für L-Cladinosylgruppe der Formel (II) steht, R^2 für Trimethylsilylgruppe steht, R^3 und R^8 einander gleich sind und für Wasserstoff stehen, R^4 und R^5 einander gleich sind und für Benzyloxycarbonylgruppe stehen, R^6 für Hydroxylgruppe steht und R^7 Methyl ist, und einer Verbindung der allgemeinen Formel (I), worin R^1 für L-Cladinosylgruppe der Formel (II) steht, R^2 für Trimethylsilylgruppe steht, R^3 und R^7 einander gleich sind und für Wasserstoff stehen, R^4 und R^5 einander gleich sind und für Benzyloxycarbonylgruppe stehen, R^6 für Hydroxylgruppe steht und R^8 Methyl ist, erhalten wird,

welche anschließend der Entschützung von Schutzgruppen in 2'- und 3'-Stellungen in einer Lösung von niedrigen Alkoholen, vorzugsweise Ethanol, in Anwesenheit des NaOAc/HOAc Puffer (pH 5) und eines Katalysators in Wasserstoffatmosphäre bei einem Druck von 1-20 Bar und dann, nach der Isolierung, einer Desilylierung in 4"-und 11-Stellungen in niedrigen Alkoholen, vorzugsweise Isopropanol, in Anwesenheit von Ameisensäure unterworfen werden, wobei im Fall von

A/ eine Verbindung der allgemeinen Formel (I), worin R^1 für L-Cladinosylgruppe der Formel (II) steht, R^2, R^3, R^4, R^5 und R^7 einander gleich sind und für Wasserstoff stehen, R^6 Hydroxylgruppe ist und R^8 Methyl ist, erhalten wird, oder im Fall von

B/ ein Gemisch einer Verbindung der allgemeinen Formel (I), worin R^1 für L-Cladinosylgruppe der Formel (II) steht, R^2, R^3, R^4, R^5 und R^8 einander gleich sind und für Wasserstoff stehen, R^6 für Hydroxylgruppe steht und R^7 Methyl ist, und einer Verbindung der allgemeinen Formel (I), worin R^1, R^2, R^3, R^4, R^5, R^7 und R^8 die für die Entschützung im Fall von **A/** angegebenen Bedeutungen haben, erhalten wird,

welche anschließend einer reduktiven 3'-N-Methylierung mit 1 - 3 Äquivalenten von Formaldehyd (37 %) in Anwesenheit einer gleichen oder zweifachen Menge von Ameisensäure (98-100 %) und eines Hydrierungskatalysators oder einer anderen Wasserstoffquelle, in einem reaktionsinerten Lösungsmittel, vorzugsweise Chloroform, bei erhöhter Temperatur, vorzugsweise bei Rückflußtemperatur, unterworfen werden, wobei im Fall von

A/ eine Verbindung der allgemeinen Formel (I), worin R^1 für L-Cladinosylgruppe der Formel (II) steht, R^2, R^3, R^4 und R^7 einander gleich sind und für Wasserstoff stehen, R^5 und R^8 einander gleich sind und für Methyl stehen und R^6 Hydroxylgruppe ist, erhalten wird, oder im Fall von

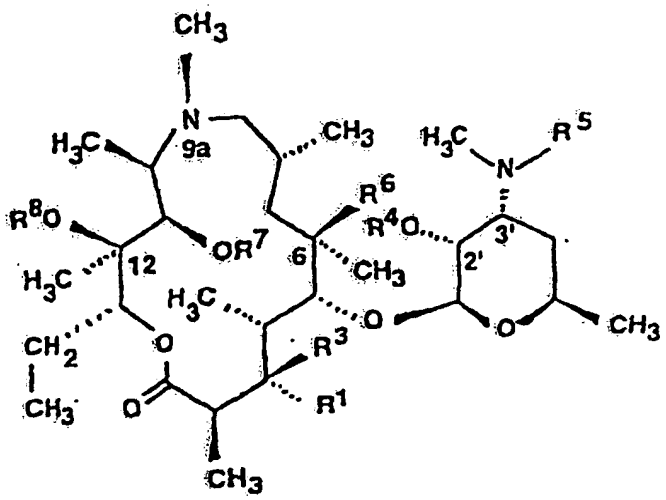
B/ ein Gemisch einer Verbindung der allgemeinen Formel (I), worin R^1 für L-Cladinosylgruppe der Formel (II) steht, R^2, R^3, R^4 und R^8 einander gleich sind und für Wasserstoff stehen, R^5 und R^7 einander gleich sind und für Methyl stehen und R^6 Hydroxylgruppe ist, und einer Verbindung der allgemeinen Formel (I), worin R^1, R^2, R^3, R^4, R^5, R^7 und R^8 die für 3'-*N*-Methylierung im Fall von **A/** angegebenen Bedeutungen haben, erhalten wird, das dann gegebenenfalls einer Trennung auf einer Silikagelsäule unterworfen wird, wobei eine chroma-

tographisch homogene Verbindung der allgemeinen Formel (I), worin R^1 für L-Cladinosylgruppe steht, R^2, R^3, R^4 und R^8 einander gleich sind und für Wasserstoff stehen, R^5 und R^7 einander gleich sind und für Methyl stehen und R^6 für Hydroxylgruppe steht (11-*O*-Methylazithromycin), und eine Verbindung der allgemeinen Formel (I), worin R^1, R^2, R^3, R^4, R^5, R^6, R^7 und R^8 die für 3'-*N*-Methylierung im Fall von A/angegebenen Bedeutungen haben (12-*O*-Methylazithromycin), erhalten werden.

8. Pharmazeutische Zubereitung, anwendbar bei der Behandlung von bakteriellen Infektionen bei Menschen und Tieren, die antibakteriell wirksame Mengen der Verbindung der allgemeinen Formel (I) oder deren pharmazeutisch annehmbaren Additionssalzen gemäß Anspruch 1 in einer Kombination mit einem pharmazeutisch annehmbaren Träger umfasst.

Revendications

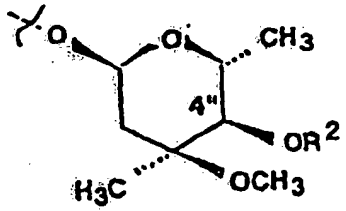
1. Composé de la formule générale (I) :



(I)

caractérisé en ce que :

R^1 représente un groupe L-cladinosyle de la formule (II) :



(II)

dans laquelle :

R^2 représente individuellement un groupe silyle,
R^3 représente individuellement de l'hydrogène,
R^4 représente individuellement de l'hydrogène ou un groupe $-COO-(CH_2)_n-Ar$, dans lequel n vaut 1-7 et Ar représente individuellement un groupe aryle non substitué ou substitué comportant jusqu'à 18 atomes de carbone,
R^5 représente individuellement de l'hydrogène, un groupe méthyle ou un groupe $-COO-(CH_2)_n-Ar$, dans lequel

n vaut 1-7 et Ar représente individuellement un groupe aryle non substitué ou substitué comportant jusqu'à 18 atomes de carbone,
R^6 représente individuellement un groupe hydroxyle,
R^7 représente individuellement de l'hydrogène, un groupe alkyle en C_1-C_{12}, un groupe silyle,
R^8 représente individuellement de l'hydrogène, un groupe alkyle en C_1-C_{12},

et ses sels d'addition pharmaceutiquement acceptables avec des acides inorganiques ou organiques.

2. Composé suivant la revendication 1, **caractérisé en ce que** R^1 représente un groupe L-cladinosyle, R^2 et R^7 sont mutuellement identiques et représentent un groupe triméthylsilyle, R^3 et R^8 sont mutuellement identiques et représentent de l'hydrogène, R^4 et R^5 sont mutuellement identiques et représentent un groupe benzyloxycarbonyle et R^6 est un groupe hydroxyle.

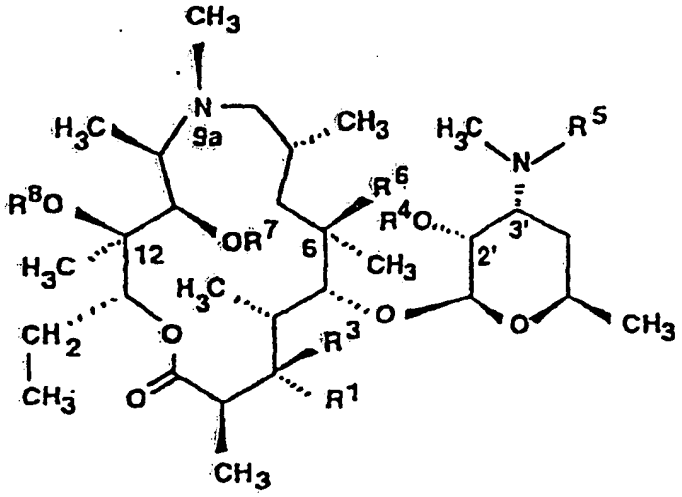
3. Composé suivant la revendication 1, **caractérisé en ce que** R^1 représente un groupe L-cladinosyle, R^2 représente un groupe triméthylsilyle, R^3, R^7 et R^8 sont mutuellement identiques et représentent de l'hydrogène, R^4 et R^5 sont mutuellement identiques et représentent un groupe benzyloxycarbonyle et R^6 est un groupe hydroxyle.

4. Composé suivant la revendication 1, **caractérisé en ce que** R^1 représente un groupe L-cladinosyle, R^2 et R^7 sont mutuellement identiques et représentent un groupe triméthylsilyle, R^3 représente de l'hydrogène, R^4 et R^5 sont mutuellement identiques et représentent un groupe benzyloxycarbonyle, R^6 est un groupe hydroxyle et R^8 est du méthyle.

5. Composé suivant la revendication 1, **caractérisé en ce que** R^1 représente un groupe L-cladinosyle, R^2 représente un groupe triméthylsilyle, R^3 et R^8 sont mutuellement identiques et représentent de l'hydrogène, R^4 et R^5 sont mutuellement identiques et représentent un groupe benzyloxycarbonyle, R^6 représente un groupe hydroxyle et R^7 est du méthyle.

6. Composé suivant la revendication 1, **caractérisé en ce que** R^1 représente un groupe L-cladinosyle, R^2 représente un groupe triméthylsilyle, R^3 et R^7 sont mutuellement identiques et représentent de l'hydrogène, R^4 et R^5 sont mutuellement identiques et représentent un groupe benzyloxycarbonyle, R^6 est un groupe hydroxyle et R^8 est du méthyle.

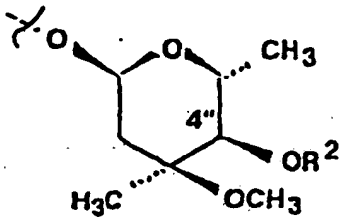
7. Procédé de préparation de 12-O-méthylazithromycine et/ou de 11-O-méthylazithromycine et de leurs sels d'addition pharmaceutiquement acceptables avec des acides inorganiques ou organiques, **caractérisé en ce qu'**une azithromycine de la formule (I) :



(I)

dans laquelle :

R^1 représente individuellement un groupe L-cladinosyle de la formule (II) :



(II)

et R^2, R^3, R^4, R^7 et R^8 sont mutuellement identiques et représentent de l'hydrogène, R^5 est du méthyle et R^6 est un groupe hydroxyle, est soumise à une réaction avec des chlorures d'acide carboxylique organiques de la formule (III) :

$$ClCOO(CH_2)_n\text{-}Ar \qquad (III)$$

dans laquelle n vaut 1-7 et Ar représente individuellement un groupe aryle non substitué ou substitué comportant jusqu'à 18 atomes de carbone, avantageusement avec du chlorure de benzyloxycarbonyle, en présence de bases, avantageusement du bicarbonate de sodium, dans un solvant inerte vis-à-vis de la réaction, avantageusement dans du benzène ou du toluène, pour donner un composé de la formule générale (I), dans laquelle R^1 représente un groupe L-cladinosyle de formule (II), R^2, R^3, R^7 et R^8 sont mutuellement identiques et représentent de l'hydrogène, R^4 et R^5 sont mutuellement identiques et représentent un groupe benzyloxycarbonyle et R^6 est un groupe hydroxyle,

qui est ensuite soumise à une silylation sélective des groupes hydroxyle en

A) les positions 4" et 11 avec un excès 2-5 équimolaire d'un agent de silylation, avantageusement avec un mélange de chlorure de triméthylsilyle et de triméthylsilyl imidazole, dans un solvant inerte organique tel que la pyridine, l'acétate d'éthyle, le N,N-diméthyl formamide ou le chlorure de méthylène, avantageusement dans de la pyridine, à une température de 0-5°C pendant 5-8 heures, pour donner un composé de la formule générale (I), dans laquelle R^1 représente un groupe L-cladinosyle de la formule (II), R^2 et R^7 sont mutuellement identiques et représentent un groupe triméthylsilyle, R^3 et R^8 sont mutuellement identiques et représentent de l'hydrogène, R^4 et R^5 sont mutuellement identiques et représentent un groupe benzyloxycarbonyle et R^6 est un groupe hydroxyle, ou en

B) la position 4" avec un excès 1,1-2 équimolaire d'un agent de silylation, dans un solvant inerte organique, avantageusement de la pyridine, à une température de 0-5°C, pendant 1 heure, pour donner un composé de la formule générale (I), dans laquelle R^1 représente un groupe L-cladinosyle de la formule (II), R^2 représente un groupe triméthylsilyle, R^3, R^7 et R^8 sont mutuellement identiques et représentent de l'hydrogène, R^4 et R^5 sont mutuellement identiques et représentent un groupe benzyloxycarbonyle et R^6 représente un groupe hydroxyle,

qui sont ensuite soumis à une O-alkylation avec un excès 1,3 à 10 molaires d'un agent d'alkylation correspondant, avantageusement un agent de méthylation, avantageusement de l'iodure de méthyle en présence de 1,1-8,5 moles d'une base appropriée comme les hydrures de métal alcalin, avantageusement de l'hydrure de sodium, dans un solvant inerte vis-à-vis de la réaction comme le diméthylsulfoxyde, le tétrahydrofuranne, le N,N-diméthyl formamide ou un mélange de ceux-ci, à une température allant de -15°C à la température ambiante, avantageusement à 0-5°C, pour donner dans le cas de :

A) un composé de la formule générale (I), dans laquelle R^1 représente un groupe L-cladinosyle de la formule (II), R^2 et R^7 sont mutuellement identiques et représentent un groupe triméthylsilyle, R^3 représente de l'hydrogène, R^4 et R^5 sont mutuellement identiques et représentent un groupe benzyloxycarbonyle, R^6 est un groupe hydroxyle et R^8 est du méthyle, ou dans le cas de :

B) un mélange d'un composé de la formule générale (I), dans laquelle R^1 représente un groupe L-cladinosyle de la formule (II), R^2 représente un groupe triméthylsilyle, R^3 et R^8 sont mutuellement identiques et représen-

tent de l'hydrogène, R^4 et R^5 sont mutuellement identiques et représentent un groupe benzyloxycarbonyle, R^6 représente un groupe hydroxyle et R^7 est du méthyle, et d'un composé de la formule générale (I), dans laquelle R^1 représente un groupe L-cladinosyle de la formule (II), R^2 représente un groupe triméthylsilyle, R^3 et R^7 sont mutuellement identiques et représentent de l'hydrogène, et R^4 et R^5 sont mutuellement identiques et représentent un groupe benzyloxycarbonyle, R^6 est un groupe hydroxyle et R^8 est du méthyle,

qui sont alors soumis à une déprotection des groupes de protection aux positions 2' et 3' dans une solution d'alcools inférieurs, avantageusement de l'éthanol, en présence d'un tampon de NaOAc/HOAc (pH 5) et d'un catalyseur dans une atmosphère d'hydrogène à une pression de 1-20 bars et ensuite après isolement, à une désilylation aux positions 4" et 11 dans des alcools inférieurs, avantageusement de l'isopropanol, en présence d'acide formique, pour donner dans le cas de :

A) un composé de la formule générale (I), dans laquelle R^1 représente un groupe L-cladinosyle de la formule (II), R^2, R^3, R^4, R^5 et R^7 sont mutuellement identiques et représentent de l'hydrogène, R^6 est un groupe hydroxyle et R^8 est du méthyle, ou dans le cas de :
B) un mélange d'un composé de la formule générale (I), dans laquelle R^1 représente un groupe L-cladinosyle de la formule (II), R^2, R^3, R^4, R^5 et R^8 sont mutuellement identiques et représentent de l'hydrogène, R^6 est un groupe hydroxyle et R^7 est du méthyle, et d'un composé de la formule générale (I), dans laquelle R^1, R^2, R^3, R^4, R^5, R^7 et R^8 ont les significations telles que données pour la déprotection dans le cas de A),

qui sont alors soumis à une 3'-N-méthylation réductive avec 1-3 équivalents de formaldéhyde (37%) en présence d'une quantité égale ou double d'acide formique (98-100%) et d'un catalyseur d'hydrogénation ou de toute autre source d'hydrogène, dans un solvant inerte vis-à-vis d'une réaction, avantageusement du chloroforme, à une température élevée, avantageusement à la température de reflux, pour donner dans le cas de :

A) un composé de la formule générale (I), dans laquelle R^1 représente un groupe L-cladinosyle de la formule (II), R^2, R^3, R^4 et R^7 sont mutuellement identiques et représentent de l'hydrogène, R^5 et R^8 sont mutuellement identiques et représentent du méthyle et R^6 est un groupe hydroxyle, ou dans le cas de :
B) un mélange d'un composé de la formule générale (I), dans laquelle R^1 représente un groupe L-cladinosyle de la formule (II), R^2, R^3, R^4 et R^8 sont mutuellement identiques et représentent de l'hydrogène, R^5 et R^7 sont mutuellement identiques et représentent du méthyle, et R^6 est un groupe hydroxyle, et d'un composé de la formule générale (I), dans laquelle R^1, R^2, R^3, R^4, R^5, R^7 et R^8 ont les significations telles que données pour la 3'-N-méthylation dans le cas A), qui est ensuite éventuellement soumis à une séparation sur une colonne de gel de silice, pour donner un composé chromatographiquement homogène de la formule générale (1), dans laquelle R^1 représente un groupe L-cladinosyle, R^2, R^3, R^4 et R^8 sont mutuellement identiques et représentent de l'hydrogène, R^5 et R^7 sont mutuellement identiques et représentent du méthyle et R^6 représente un groupe hydroxyle (11-O-méthylazithromycine) et un composé de la formule générale (1), dans laquelle R^1, R^2, R^3, R^4, R^5, R^6, R^7 et R^8 ont les significations telles que données pour la 3'-N-méthylation dans le cas de A) (12-O-méthylazithromycine).

8. Composition pharmaceutique utilisable dans le traitement d'infections bactériennes chez les êtres humaines et les animaux comprenant des quantités antibactériennement efficaces du composé de la formule générale (I) ou de ses sels d'addition pharmaceutiquement acceptables suivant la revendication 1, en une combinaison avec un support pharmaceutiquement acceptable.